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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/654,276	09/01/2000	Smadar Cohen	9124.117US01	5848

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/654,276	COHEN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9,10 and 16-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9,10 and 16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/23/03 has been entered. Claims 1-3,5,6,9,10 and 16-21 are currently pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1-3, 5-6, 9-10, and 16-21 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The previous office actions have stated that while the specification provides an enabling disclosure for growing fetal or autologous cardiomyocytes alone or in the presence of fetal or autologous endothelial cells, fibroblasts, or smooth muscle cells on an alginate scaffold and

using the resulting biografts to treat cardiac damage, the specification does not provide an enabling disclosure for making and using biograft alginate scaffolds which do not comprise fetal or autologous cardiomyocytes to produce cardiac-like tissue and repair cardiac damage. The applicant argues that cardiomyocytes are not essential for the production of cardiac like tissue and the repair of cardiac damage. The applicant states that example 2 in the instant specification discloses the seeding and growth of fetal aortic endothelial cells into cord-like structures in the absence of cardiomyocytes on the alginate scaffold *in vitro*. Based on this data, the applicant argues that cardiomyocytes are not essential. In response, the office does not dispute that example 2 disclose the growth of fetal aortic endothelial cells into cord-like structures in the absence of cardiomyocytes on the disclosed alginate scaffold. However, the claimed methods and the disclosed use of the alginate scaffold in the specification are directed to the treatment of myocardial damage. The specification clearly teaches that one of the relevant features of the instant invention is the formation of a contracting cardiac-like tissue (specification, page 4, lines 24-29). In embodiments where endothelial cells are present, the specification clearly teaches that the endothelial cells are included to form capillary-like structures which improve the integration and vascularization of the functional cells (specification, page 8, lines 15-30). From the context of the specification, it is clear that the functional cells referred to are cardiomyocytes. This is also clear from the actual *in vivo* working examples which utilize biografts according to the instant invention which comprise fetal cardiomyocytes and which are capable of forming cardiac like tissue, see examples 1, and examples 4-8 in the instant specification. Example 2 does not demonstrate any therapeutic effect deriving from the cultured endothelial cells or demonstrate that an alginate scaffold comprising cord-like endothelial cell aggregates are capable of

producing cardiac like tissue or having any effect on myocardial damage. As stated in the previous office actions, endothelial cells do not share the same properties as cardiomyocytes, particularly spontaneous contractility and ability to spread cardiac electrical impulses. Thus, based on the nature of endothelial cells versus cardiomyocytes, the particular teachings of the specification as to the importance of biografts comprising cardiac-like tissue and the importance of cardiomyocytes in producing cardiac-like tissue in the alginate scaffolds, the lack of correlation between the cord-like structures exemplified in example 2 and contracting cardiac-like tissue, the lack of correlation between the *in vitro* growth of endothelial cell cord-like structures and the repair of cardiac damage *in vivo*, and the breadth of claims, it would have required undue experimentation to practice the invention as claimed using endothelial cells in the absence of cardiomyocytes.

In regards to other cellular embodiments of the invention, the applicant argues that embryonic and mesenchymal stem cells are enabled for use in the instant invention. The applicant has submitted an article by Tomita et al., published in 1999, as evidence that the skilled artisan would have known at the time of filing how to promote differentiation of stem cells into cardiomyocytes. In response, the office notes that Tomita et al. teaches a method of promoting the differentiation of bone marrow cells into cardiac-like cells *in vitro* comprising culturing the cells with 5-azacytidine. Tomita et al. further teaches that transplantation of bone marrow cells cultured with 5-azacytidine are able to improve myocardial function following cryoinjury whereas freshly isolated bone marrow cells or bone marrow cells cultured without 5-azacytidine did not improve myocardial function. The methods taught by Tomita et al. are not analogous to those disclosed by the applicants. The applicant claims and specification teach the use of

mesenchymal or embryonic stem cells. Tomita et al. teaches the use of adult bone marrow which clearly does not contain embryonic stem cells and which may or may not comprise any mesenchymal stem cells. Thus, the cell population of Tomita et al. does not correlate to the cell populations claimed by the applicants. Further, Tomita et al. clearly teaches differentiating the bone marrow cells into cardiac like cells using 5-azacytidine in *in vitro* culture. Tomita et al. does not teach or even speculate that 5-azacytidine would be able to differentiate any other type of cells into cardiac-like cells. The specification does not disclose the use of 5-azacytidine or the use of bone marrow cells. Thus, a nexus cannot be made between the teachings of Tomita et al. and the teachings of the specification. The applicant is also reminded that the Federal Circuit states:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. *Genentech Inc. v. Novo Nordisk* A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Furthermore, the previous office actions have stated that while embryonic stem cells and mesenchymal stem cells have the genetic **potential** to develop into cardiac myocytes, these progenitor cells also have the capacity to develop into a number of other different non-muscle cells. The specification fails to provide any guidance as to the particular combination of factors and conditions necessary to promote the differentiation and development of embryonic or

mesenchymal stem cells into cardiac myocytes or myoblasts. The specification only identifies two growth factors, VEGF and FGF, which have been reported in the prior art to be capable of stimulating angiogenesis, not the differentiation of embryonic or mesenchymal stem cells into cardiac myocytes. The specification does not identify any growth factor or combination of growth factors capable of promoting the growth and differentiation of any type of stem cell. Further, the specification does not teach which combination of factors, or their necessary concentrations, are capable of causing the differentiation of stem cells into any particular cell type. In the absence of any specific teachings, the office maintains that it would require undue experimentation to determine the conditions under which embryonic or mesenchymal stem cells can be induced to differentiate into muscle cells *in vitro* or *in vivo*.

The applicant further argues that the specification's disclosure provides sufficient guidance for the use of syngeneic, allogeneic, or xenogeneic cells in the invention as claimed. It is noted that the applicant has re-amended the claims to remove the limitation added by the after-final amendment to the use of mammalian cells " of the same species". Thus, the claims as amended read on the use of syngeneic, allogeneic, or xenogeneic cells. The previous office actions have noted that the specification's working examples which utilize allogeneic cells used fetal allogeneic cells. The prior art teaches that fetal cells are substantially less immunogenic than their adult counterparts, and that as a result, fetal allografts are less susceptible to graft rejection. For this reason, the scope of enablement was indicated to include fetal cardiomyocytes without any limitation to their origin. However, adult tissue, as discussed in detail in previous office actions, is subject to substantial allogeneic or xenogeneic immune responses which severely limit the ability of the cells to survive in the host and render any therapeutic benefit (Li

et al., and Kaufman et al.). The specification does not provide any guidance as to measures or methods necessary to prevent destructive allogeneic or xenogeneic immune responses following the transplantation of the matrix containing allogeneic or xenogeneic tissue. Therefore, in view of the evidence of record, the applicant's statement that the specification does provide sufficient guidance to use allogeneic or xenogeneic cells is not compelling in the absence of any supporting evidence or arguments.

Therefore, for reasons of record as discussed in detail above, the specification fails to provide an enabling disclosure for the scope of applicant's invention as claimed.

No claims are allowed.

This is an RCE of applicant's earlier Application No. 09/654,276. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER